ALNYLAM PHARMACEUTICALS, INC.
Form 10-K
February 14, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2018

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission File Number 001-36407

ALNYLAM PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	77-0602661
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

300 Third Street, Cambridge, MA 02142

(Address of Principal Executive Offices) (Zip Code)

Registrant’s telephone number, including area code: (617) 551-8200

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $0.01 par value per share	The Nasdaq Global Select Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer
Non-accelerated filer	Smaller reporting company
	Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes No

The aggregate market value of the registrant's common stock, $0.01 par value per share ("Common Stock"), held by non-affiliates of the registrant, based on the last sale price of the Common Stock at the close of business on June 29, 2018, was $9,819,826,967. For the purpose of the foregoing calculation only, all directors and executive officers of the registrant are assumed to be affiliates of the registrant.

At January 31, 2019, the registrant had 106,258,250 shares of Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2019 annual meeting of stockholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2018, are incorporated by reference into Part II, Item 5 and Part III of this Form 10-K.

ALNYLAM PHARMACEUTICALS, INC.

ANNUAL REPORT ON FORM 10-K

For the Year Ended December 31, 2018

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This annual report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, that involve risks and uncertainties. All statements other than statements relating to historical matters should be considered forward-looking statements. When used in this report, the words “believe,” “expect,” “plan,” “anticipate,” “estimate,” “predict,” “may,” “could,” “should,” “intend,” “will,” “target,” “goal” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Our actual results could differ materially from those discussed in the forward-looking statements as a result of a number of important factors, including the factors discussed in this annual report on Form 10-K, including those discussed in Item 1A of this report under the heading “Risk Factors,” and the risks discussed in our other filings with the Securities and Exchange Commission. Readers are cautioned not to place undue reliance on these forward-looking statements, which reflect management’s analysis, judgment, belief or expectation only as of the date hereof. We explicitly disclaim any obligation to update these forward-looking statements to reflect events or circumstances that arise after the date hereof.

PART I

ITEM 1. BUSINESS

Overview

We are a global commercial-stage biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. RNAi is a naturally occurring biological pathway within cells for sequence-specific silencing and regulation of gene expression. By harnessing the RNAi pathway, we have developed a new class of innovative medicines, known as RNAi therapeutics. RNAi therapeutics are comprised of small interfering RNA, or siRNA, and function upstream of conventional medicines by potently silencing messenger RNA, or mRNA, that encode for disease-causing proteins, thus preventing them from being made. We believe this is a revolutionary approach with the potential to transform the care of patients with genetic and other diseases. Our efforts to advance this revolutionary approach culminated with the approval in 2018 of the first ever RNAi therapeutic, ONPATTRO® (patisiran), for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis, or hATTR amyloidosis, in adults in the U.S. and for the treatment of hATTR amyloidosis in adult patients with Stage 1 or Stage 2 polyneuropathy in the European Union, or EU.

Our research and development strategy is to target genetically validated genes that have been implicated in the cause or pathway of human disease. We utilize a lipid nanoparticle (LNP) or N-acetylgalactosamine (GalNAc) conjugate approach to enable hepatic delivery of siRNAs. For delivery to the central nervous system, or CNS, and the eye (ocular delivery), we intend to utilize an alternative conjugate approach. Our focus is on clinical indications where there is a high unmet need, early biomarkers for the assessment of clinical activity in Phase 1 clinical studies, and a definable path for drug development, regulatory approval, patient access and commercialization.

We are committed to the advancement of our Alnylam 2020 strategy of building a multi-product, commercial biopharmaceutical company with a sustainable pipeline of RNAi therapeutics to address the needs of patients who have limited or inadequate treatment options. Specifically, our broad pipeline of investigational RNAi therapeutics is focused in four Strategic Therapeutic Areas, or “STArs:” Genetic Medicines; Cardio-Metabolic Diseases; Hepatic Infectious Diseases; and CNS/Ocular Diseases. In August 2018, we received regulatory approval for ONPATTRO from the United States Food and Drug Administration, or FDA, for the treatment of the polyneuropathy of hATTR amyloidosis in adults. Also, in August 2018, the European Commission, or EC, granted marketing authorisation for ONPATTRO for the treatment of hATTR amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy. We began

selling ONPATTRO in the U.S. in August 2018 and in Germany in October 2018, and are now marketing ONPATTRO in several additional countries in Europe. During 2018, we also submitted regulatory applications for the approval of ONPATTRO in Japan, Canada and Switzerland. Regulatory filings in additional markets in Europe and elsewhere are planned throughout 2019.

In addition to our first marketed product, we have five late-stage investigational programs advancing toward potential commercialization. These programs include our wholly owned programs: givosiran for the treatment of acute hepatic porphyria, or AHP, lumasiran for the treatment of primary hyperoxaluria type 1, or PH1, and vutrisiran for the treatment of ATTR amyloidosis. Inclisiran for the treatment of hypercholesterolemia and atherosclerotic cardiovascular disease, or ASCVD is being advanced by our partner, The Medicines Company, or MDCO, and fitusiran for the treatment of hemophilia is being advanced by our partner Sanofi Genzyme, the specialty care global business unit of Sanofi.

Based on our expertise in RNAi therapeutics and broad intellectual property estate, we have formed alliances with leading pharmaceutical and life sciences companies to support our development and commercialization efforts, including Sanofi Genzyme, MDCO, Vir Biotechnology, Inc., or Vir, and Regeneron Pharmaceuticals, Inc., or Regeneron.

Key 2018 and Recent Highlights

Commercial/Late Stage Pipeline

- ONPATTRO (patisiran) – hATTR Amyloidosis

Commercial Highlights

- Launched ONPATTRO in the U.S. in August 2018 and in several countries in Europe during the fourth quarter of 2018
- Recognized ONPATTRO net revenue of $12.5 million for the year ended December 31, 2018

R&D Highlights

- Received FDA approval of ONPATTRO for the treatment of the polyneuropathy of hATTR amyloidosis in adults
- Received marketing authorisation from the EC for ONPATTRO for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy
- Submitted a new drug application, or NDA, to Japan's Pharmaceuticals and Medical Devices Agency, or PMDA
- Received a Priority Review designation in Canada
- Submitted a marketing authorisation application, or MAA, to The Swiss Agency for Therapeutic Products

- Vutrisiran (ALN-TTRsc02) – ATTR Amyloidosis

- Initiated the HELIOS-A Phase 3 study
- Received Orphan Drug Designations, or ODDs, from U.S. and EU regulatory agencies

- Givosiran – Acute Hepatic Porphyria
- Completed enrollment in the ENVISION Phase 3 study, with 94 patients across 36 sites in 18 countries
- Reported positive topline results from the ENVISION interim efficacy analysis
- Initiated a rolling submission of an NDA to the FDA

- Lumasiran – Primary Hyperoxaluria Type 1
- Received Breakthrough Therapy and Priority Medicines Designations from the U.S. and EU regulatory authorities, respectively
- Initiated the ILLUMINATE-A Phase 3 study of lumasiran in children and adults with PH1
- Aligned with the FDA on trial design for ILLUMINATE-B, a Phase 3 pediatric study in PH1 patients less than six years of age

- Fitusiran - Hemophilia (in collaboration with Sanofi Genzyme)
- Initiated enrollment into the ATLAS Phase 3 studies

- Inclisiran – Hypercholesterolemia (in collaboration with MDCO)
- Advanced ORION Phase 3 program; received recommendation from the Independent Data Monitoring Committee, or DMC, to continue the ongoing Phase 3 ORION trials as designed and to be conducted without modification, following the fifth review of unblinded safety and efficacy data
- Accumulated more than 2,450 years of patient safety data as of January 7, 2019

Early to Mid-Stage Pipeline

- Cemdisiran for the treatment of complement-mediated diseases; discontinued Phase 2 study in atypical hemolytic uremic syndrome, or aHUS, due to recruitment challenges and obtained regulatory approval to initiate a Phase 2 study in IgA nephropathy
- ALN-AAT02 for the treatment of alpha-1 liver disease, which is based on our Enhanced Stabilization Chemistry-Plus, or ESC+, GalNAc conjugate technology; obtained approval of a clinical trial application, or CTA, and initiated a Phase 1/2 study
- ALN-HBV02 (VIR-2218) for the treatment of chronic hepatitis B virus, or HBV, infection; initiated dosing in a Phase 1/2 study in collaboration with our partners at Vir

Corporate Highlights

- Finance
  - Ended 2018 with $1.13 billion in cash, cash equivalents, and marketable debt securities and restricted investments, excluding equity securities
- Business
  - Completed a strategic restructuring of our rare disease alliance with Sanofi Genzyme, originally formed in 2014, with us obtaining global rights to our ATTR amyloidosis programs – ONPATTRO and vutrisiran – and Sanofi Genzyme obtaining global rights to fitusiran
  - Formed a strategic collaboration with Regeneron to identify and advance RNAi therapeutics for the treatment of nonalcoholic steatohepatitis, or NASH, a chronic liver disease
- Public Offering
  - In January 2019, sold 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of $77.50 per share, receiving aggregate net proceeds of approximately $382 million

RNAi Therapeutics – A New Class of Innovative Medicines

RNAi is a natural cellular process that was discovered in 1998 and was recognized with the award of the 2006 Nobel Prize for Physiology and Medicine to Dr. Andrew Fire and Dr. Craig Mello.

RNAi therapeutics harness the natural RNAi pathway to silence disease-associated genes and knock down production of proteins implicated in disease, representing the opportunity to create a new class of innovative medicines. RNAi therapeutics exert their biological effects through a highly potent, catalytic mechanism. This unique mechanism of action confers a number of attributes that we believe have the potential to provide meaningful differentiation and distinct value for our RNAi therapeutics relative to other drug classes.

Key Features of Alnylam Investigational RNAi Therapeutics Potential Attributes for Differentiation and Value
• Potential to silence any disease-associated gene, including so-called “undruggable” targets, where conventional therapeutic modalities (e.g., small molecule drugs and biologics) have not been successful
• Demonstrated potential in clinical trials to achieve robust clinical activity with up to 99 percent target gene knockdown in some cases
• Sustained pharmacodynamic effect that has potential to provide improved and consistent efficacy compared with intermittent and transient effects often achieved with other drug classes
• Demonstrated durability of effect in clinical trials that enables once-monthly, once-quarterly and, in some cases, possible bi-annual dose regimens
• Ability to be administered via subcutaneous injection when using our proprietary GalNAc-conjugate delivery platform
• Potential for room temperature stability, avoiding the inconveniences, costs and global challenges of a cold chain distribution